REMARKS

Introductory remarks

Claims 1-4, 6 and 9-16 were pending before the Office. By this Amendment, Applicants have amended claims 1 and 15. Claims 9 and 14 have been cancelled. Claim 17 has been added. Thus, claims 1-4, 6, 10-13 and 15-17 shall be pending upon entry of this Amendment to the Claims.

The amendments have been made solely to claim more fully the invention or to clearly recite what Applicants regard as the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's rejections in the Office action issued in the present application. Applicants reserve the right to pursue claims as originally filed or similar claims in one or more subsequent applications.

Support for the amendments can be found throughout the application, including the specification, drawings, examples and claims, as originally filed.

Accordingly, no new matter has been added by this amendment.

Reconsideration of the subject application in view of the above amendments and following remarks is respectfully requested.

The Examiner is thanked for indicating that "the literal sequences SEQ ID NO: 1 and 2 are free of the art." See page 10 of the Office Action.

Priority

The Examiner is thanked for acknowledging Applicants' entitlement to the benefit of the filing date of German application No. 10257354.9, filed December 9, 2002.

The rejections under 35 U.S.C. § 112, first paragraph (written description), are overcome

The Examiner has maintained the rejection of claims 1-4, 6 and 9-12 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement based on reasons already of record and further comments stated in the instant Office Action. The

Examiner has also extended this rejection to claims 13 (formerly claim 7) and claim 16 (formerly claim 8) and new claims 14-15.

As an initial matter, without wishing to acquiesce as to the Examiner's rejections, claims 9 and 14 have been cancelled, without prejudice, in the interest of advancing prosecution. Accordingly, the rejection as it applies to claim 9 and 14 is now moot. Thus, claims 1-4, 6, 10-13 and 15 remain rejected.

Essentially, the Examiner contends that written description is not provided because the claims encompass a genus of nucleic acid molecules encoding polypeptides having at least 95% identity to SEQ ID NO: 2 "without disclosure about which nucleotides can vary from SEQ ID NO: 1 (and its corresponding polypeptides SEQ ID NO: 2) and still retain the claimed activity." See page 9 of the Office Action. The Examiner further contends that written description is lacking with regard to the genus of nucleic acid molecule defined by hybridization conditions because such a genus "embraces sub-sequences that are unknown and [would] include unsequenced polynucleotides, whose function is yet to be determined. The nucleic acids might also encompass very large nucleic acids that hydridize under highly stringent conditions only over a short range near one end of both sequences. In this case, there would be a very low level of homology between the two sequences, despite high stringency hydridization."

Applicants disagree with the Examiner's assertions. The Examiner's rejection as to written description no longer applies in view of the amendments to the claims. Particularly, claims 1 and 15 have been similarly amended to combine the requirements of sub-parts (c) (pertaining to hybridization requirements) and (d) (pertaining to sequence identity requirements). The presently amended claims 1 and 15 now encompass a more narrow genus of nucleic acid molecules by virtue of the fact that the genus is now defined in terms of function (encodes a fluorescent protein), hybridization features (stringent conditions) and sequence identity features (95% sequence homology to SEQ ID NO: 1). Under the current written description case law, the genus of nucleic acid molecules of claims 1 and 15 (and their dependent claims) should be viewed as meeting the written description requirements.

The Federal Circuit has addressed the standard for written description as it applies to the field of biotechnology in *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), stating that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567. Addressing the manner by which a genus of cDNAs might be described, the court stated that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of ***structural features*** common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit further clarified the written description requirement as it pertains to the field of biotechnology in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (Fed. Cir. 2002). The court in *Enzo* stated that "[t]he written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics…i.e., ***complete or partial structure***, other physical and/or chemical properties, functional characteristics when ***coupled*** with a known or disclosed ***correlation between function and structure***, or some combination of such characteristics." Id. at 1324.

When the appropriate legal standard is applied to the instant claims and facts, one must conclude that claims 1 and 15—which now are defined in terms of ***structure*** (hybridization requirements, sequence identity requirements) ***coupled with function*** (encodes a fluorescent protein)—meet the requirements for written description.

In particular, claim 1 (and similarly for claim 15) now recites an isolated nucleic acid molecule, selected from the group consisting of: (a) a nucleic acid molecule encoding a polypeptide having the amino acid sequence of SEQ ID NO: 2; (b) a nucleic acid molecule comprising the sequence of SEQ ID NO: 1; (c) a nucleic acid molecule which is at least ***95% homologous*** to SEQ ID NO: 1 whose complementary strand ***hybridizes under stringent conditions*** with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1 ***and***

which ***encodes a fluorescent protein***. The genus of nucleic acid molecules is now defined more narrowly in terms of ***structure*** (hybridization requirements, sequence identity requirements) ***coupled with function*** (encodes a fluorescent protein) and thus, meet the requirements for written description.

Here, claim 1 (and similarly as to claim 15), includes a genus of nucleic acid molecules which is at least ***95% homologous*** to SEQ ID NO: 1 whose complementary strand ***hybridizes under stringent conditions*** with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1 ***and*** which ***encodes a fluorescent protein***. The structure of SEQ ID NO: 2 is expressly disclosed in the application, as is the nucleic acid sequence of SEQ ID NO: 1. Thus, their specific structures are well-defined. Because nucleic acid molecules which hybridize under stringent conditions to a defined sequence are expected to have complementary sequences, due to Watson-Crick pairing of nucleotide bases, their structures, too, are necessarily well-defined. In addition, the nucleic acid molecules must also encode a fluorescent protein. Like enzymatic activity, fluorescence of a protein can easily be tested and observed and is a functional property of such a protein. Further structural requirements of the genus are defined by the requirement that the nucleic acid molecules are 95% homologous to SEQ ID NO: 1. Since the claims couple complete or partial structure of the genus of nucleic acids molecules (defined by both hybridization and sequence homology) together with a specific functional feature of the encoded proteins (fluorescence activity), the genus of claims 1 and 15 clearly meets the written description requirements under *Enzo*.

In view of the above, the Examiner's concern that the genus of nucleic acids "might also encompass very large nucleic acids that hybridize under highly stringent conditions only over a short range rear one end of both sequences" would no longer be true because of the structural requirement that each of the nucleic acid molecules in the genus also must have at least 95% sequence identity with SEQ ID NO: 1.

Accordingly, in view of at least the above, Applicants respectfully submit that claims 1 and 15 meet the Federal Circuit's standard for determining whether adequate written description is present.

Regarding the rejection of claim 6, which defines a genus of proteins encoded by the nucleic acid molecules of claim 1, the subject matter defined by claim 6 does not lack written description because, as shown above, the genus of nucleic acids of claim 1 possesses sufficient written description.

More in particular, the genus of proteins of claim 6 are well characterized and defined. The claimed protein is defined in terms of a protein encoded by (a) a nucleic acid which encodes SEQ ID NO: 2, (b) a nucleic acid that is SEQ ID NO: 1, or (c) a genus of nucleic acid molecules which stringently hybridizes to SEQ ID NO: 1 or to a nucleic acid encoding SEQ ID NO: 2 ***and*** which are at least 95% homologous to SEQ ID NO: 1. In each case, the encoded protein must be a fluorescent protein.

Under *Enzo*, the genus of proteins under claim 6 do not lack written description because they are defined with a specific well-defined structure (amino acid and nucleic acid sequences of fluorescent proteins) coupled to a known correlation between function (fluorescence) and structure (amino acid and nucleic acid sequences of fluorescent proteins).

Regarding the rejection of claim 10, the Examiner has maintained the allegation that the claim lacks written description on grounds of new matter because that the actual method steps recited by claim 10 were not disclosed in the instant specification as originally filed. Applicants respectfully disagree with this rejection.

Applicants maintain that claim 10 in its entirety does not constitute new matter because the recited steps of the claim are merely conventional steps well-known in the art for using any fluorescent protein as a marker gene or reporter gene ***and*** because the specification, in fact, does contain clear support for the steps of the claim. Claim 10 recites a method of determining whether a gene of interest, or fragment thereof, has been expressed comprising monitoring the

fluorescence of a polypeptide encoded by a fusion gene and comparing it to the fluorescence when the gene or fragment is not expressed, wherein said fusion gene comprises the nucleic acid of claim 1 operably linked to said gene of interest, or fragment thereof. Thus, claim 10 essentially pertains to the use of the green fluorescent protein of the invention as a reporter system. These steps are supported in the application.

For example, the specification teaches the following (but not limited to these teachings) regarding use of green fluorescent proteins as report genes:

"Reporter gene or indicator gene generally refers to genes whose gene products can be readily detected with the aid of simple biochemical or histochemical methods." (page 4)

"Reporter gene. The products of reporter genes are used as fused or nonfused indicators in genetic engineering." (page 5)

"The fluorescent protein CGFP is suitable as a reporter gene for cellular systems..." (page 8)

"The fluorescent protein CGFP is suitable as a reporter gene in bacterial and eukaryotic systems..." (page 8)

"The fluorescent protein CGFP is suitable as a fusion protein..." (page 8)

"The fluorescent protein CGFP is suitable for expression in bacterial systems..." (page 9)

"The fluorescent protein CGFP is suitable as a reporter gene in pharmacological drug screening..." (page 9)

"The fluorescent protein CGFP is suitable as a reporter coupled to nucleic acids..." (page 10)

"The fluorescent protein CGFP is suitable as a reporter coupled to proteins..." (page 10)

In addition, the specification specifically exemplifies the construction of vectors that could be used as expression vectors and reporter systems in Examples 1 and 2. Moreover, Example 3 describes the use of an expression vector containing the CGFP gene of the invention,

and inducing the expression of same, and measuring the expression level using a fluorimeter. Similar tests are carried out in Example 4 using mammalian cells and a eukaryotic expression vector.

Accordingly, in view of the above express teachings and examples in the specification, and in view of common knowledge in the art regarding the general application of green fluorescent proteins as reporter systems to monitor expression of genes, it would appear that claim 10 has the requisite amount of written descriptive support.

Accordingly, in view of at least the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-4, 6 and 9-13 and 15 35 U.S.C. § 112, first paragraph, as allegedly lacking written description support.

The rejections under 35 U.S.C. § 102(b) are overcome

The Examiner has maintained the rejection of claim 6 under 35 U.S.C. § 102(b) as allegedly being anticipated by Levine et al. ("Isolation and characterization of a photoprotein, "Phialidin", and a spectrally unique green-fluorescent protein from the bioluminescent jellyfish *Phialidium gregarium*," Comp. Biochem. Physiol., (1982), Vol. 72B, pp. 77-85). More particularly, the Examiner has maintained his assertion that the green fluorescent protein from *Phialidium gregarium* (alternatively known as *Clytia gregaria*) disclosed by LEVINE is the identical protein as the polypeptide defined by SEQ ID NO: 2 of the present invention. Applicants respectfully disagree with the rejection and traverse as follows.

The Examiner is respectfully pointed to the MPEP § 2131 which states that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Here, claim 6 is not anticipated by Levine et al. because the evidence pointed to by the Examiner does not show that Levine et al.'s green fluorescent protein is identical to the protein of SEQ ID NO: 2.

Claim 6 is directed to an isolated protein encoded by the nucleic acid molecule of claim 1. Claim 1 recites a genus of nucleic acid molecules that is defined either by (a) a nucleic acid molecule encoding a polypeptide having the amino acid sequence of SEQ ID NO: 2; (b) a nucleic acid molecule comprising the sequence of SEQ ID NO: 1; or (c) a nucleic acid molecule which is at least ***95% homologous*** to SEQ ID NO: 1 whose complementary strand ***hybridizes under stringent conditions*** with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO:2 or with a nucleic acid molecule consisting of the nucleic acid sequence of SEQ ID NO:1 ***and encodes a fluorescent protein***.

Thus, the genus of the isolated proteins of claim 6 is defined in terms of the nucleic acid molecules from which they are encoded which, in turn, are defined in terms of ***structure*** (hybridization requirements and sequence identity requirements) ***coupled with function*** (encodes a fluorescent protein). As will be shown below, the cited prior art does not teach all of the claim limitations; and thus, does not anticipate the claims.

As an initial point, Applicants have previously submitted by their March 3, 2008 Response arguments and evidence regarding significant differences in the molecular weights and spectral characteristics of the claimed polypeptides as compared to Levine et al.'s protein. Applicants hereby wish to incorporate those remarks by reference in this Response.

The Examiner fully admits that Levine et al. does not disclose either an amino acid sequence or a nucleic acid sequence anywhere in its teachings. Indeed, the Office Action states that "the Examiner agrees with the applicant's assertion that Levine et al. do not provide a nucleic acid sequence or amino acid sequence for the Green Fluorescent protein described in their reference." However, even in the absence of the actual amino acid or nucleic acid sequences of Levine et al.'s protein, the Examiner nevertheless concludes, on the basis of inherency, that Levine et al.'s protein is identical to Applicant's claimed protein, and thus, anticipates claim 6. The Office Action states that "if the Levine protein is the same protein as that of claim 6, as asserted by the examiner, then Levine would inherently satisfy the sequence related claim language."

The law of inherency dictates that a particular property (or particular protein sequence in this case) is inherent only if it ***necessarily occurs*** in the prior art. *See Atlas Powder Co. v. Ireco Inc.,* 190 F.3d 1342, 1347 (Fed. Cir. 1990). The fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert,* 9 F.3d 1531, 1534 (Fed. Cir. 1993). The Board of Patent Appeals and Interferences has emphasized that "in relying upon the theory of inherency, the examiner must provide a ***basis in fact and/or technical reasoning*** to reasonably support the determination that the allegedly inherent characteristic ***necessarily*** flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Here, the Examiner fails to provide a factual basis or technical reason that is sufficient to support the conclusion that Levine et al.'s protein is the identical protein of claim 6. To the contrary, the very evidence cited by the Examiner pertaining to the molecular weights of the proteins and their spectral characteristics tend to show that the proteins are not the same.

Regarding the discrepancy in molecular weights of the claimed and prior art proteins, the Examiner alleges that Levine et al.'s molecular weight of 57,000 +/- 4% grams/mol is somehow equivalent to the molecular weight of 26,385 grams/mol of the protein of green fluorescent protein of the invention, i.e., SEQ ID NO: 2. In particular, the Examiner alleges that the margin of error of 20-50% of Levine et al.'s molecular weight due to it being an "apparent" molecular weight renders it equivalent to Applicants' molecular weight, which was determine by a different method (x-ray crystallography). The numbers do not support this conclusion.

Levine et al.'s molecular weight of 57,000 +/- 4% grams/mol is at a minimum 54,720 grams/mol when reduced by the maximum stated 4% margin of error. This can be further reduced to a minimum of 27,360 grams/mol by taking into account the maximum margin of error of 20-50% reported by Levine et al. to be attributable to the methodology of determining an "apparent" molecular weight. Thus, the ***minimum*** molecular weight of Levine et al.'s protein attainable by accounting for all possible margin of error reported by Levine et al. is 27,360 grams/mol, which is still ***greater*** than the reported 26,385 grams/mol molecular weight of the protein of SEQ ID NO: 2.

Accordingly, even using the Examiner's logic as outlined above and under conditions most favorable to the Examiner (i.e., applying the greatest margin of error), Levine et al. still fails to teach a green fluorescent protein having the same molecular weight as Applicants' green fluorescent protein of SEQ ID NO: 2. Thus, the Examiner's reasoning should not constitute a suitable ***basis in fact and/or technical reasoning*** to support the determination that Levine et al. inherently discloses the same green fluorescent protein as claimed.

Regarding the differences in the spectral characteristics, Applicants have previously shown a comparison of the spectral characteristics between the claimed SEQ ID NO: 2 green fluorescent protein of the invention and the prior art protein of Levine et al. See page 20 of the March 3, 2008 Response. Applicants reiterate that Applicants' protein of SEQ ID NO: 2 displays a double-peak excitation profile of around 475 nm. By contrast, Levine et al.'s protein displays only a single-peak excitation profile.

The Examiner attempts to mitigate this difference by alleging that "the double-peak in the application's GFP excitation profile is not a characteristic of a single fluorescent protein." On this basis, the Examiner concludes that the spectral characteristics are essentially equivalent, despite that SEQ ID NO: 2 shows a double-peak excitation profile whereas the prior art shows a single-peak. The state of the art, however, does not support the Examiner's statement that double-peak excitation profiles do not occur.

Applicants respectfully submit Labas et al., "Diversity and evolution of the green fluorescent protein family," Proc Natl Acad Sci U S A. 2002 April 2; 99(7): 4256–4261, which clearly teaches green fluorescent proteins having double-peak excitation profiles. See Table 1, Figure 1 and page 4257, left column, lines 39-44. Thus, in view of Labas et al., the Examiner's characterization of double-peak excitation profiles is not factually correct.

Accordingly, the fact remains that the spectral data of Levine et al.'s green fluorescent protein shows a single-peak excitation profile, whereas the claimed green fluorescent protein of SEQ ID NO: 2 shows a double-peak excitation profile. Because double-peak excitation profiles of green fluorescent proteins do exist (see e.g., Labas et al.), Applicants respectfully submit that the spectral characteristics do not constitute a suitable ***basis in fact and/or technical reasoning***

that supports the determination that Levine et al. inherently discloses the same green fluorescent protein as claimed.

In view of at least the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 6 under 35 U.S.C. § 102(b).

The Examiner has also rejected claim 14 under 35 U.S.C. 102(b) as allegedly being anticipated by Fraile-Ramos et al. (Molecular Biology of the Cell, June 2001; 12: 1737-1749).

Without wishing to acquiesce as to the rejection, Applicants have cancelled claim 14, without prejudice, in the interest of advancing prosecution. Accordingly, the rejection of claim 14 is now moot.

The Examiner also rejected claim 15 under 35 U.S.C. 102(b) as allegedly being anticipated by Tsien et al. (U.S. Patent No. 5,777,079). More particularly, the Examiner contends that Tsien et al. teaches a nucleic acid molecule encoding a mutant form of GFP with excitation and emission peaks of 475 nm and 493 nm, respectively, wherein the nucleic acid molecule would no doubt hybridize under stringent conditions with a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2 or with a nucleic acid molecule of SEQ ID NO: 1.

Without wishing to acquiesce as to the rejection, Applicants have amended claim 15 to require that the claimed isolated nucleic acid molecule of part (c) is also required to have at least 95% sequence identity with SEQ ID NO: 1.

Tsien et al. does not teach (nor is it purported to teach by the Examiner) a nucleic acid molecule which has at least 95% sequence identity with SEQ ID NO: 1, in addition to the hybridization requirements; and thus, does not meet all of the claim limitations. Accordingly, Tsien et al. does not anticipate claim 15.

In view of at least the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claim 15 under 35 U.S.C. § 102(b).

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

If any issue remains as an impediment to allowance, an interview with the Examiner and SPE are respectfully requested; and, the Examiner is additionally requested to contact the undersigned to arrange a mutually convenient time and manner for such an interview.

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Respectfully submitted,

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